Crystalline methanesulfonic acid addition salts of Imatinib

Field of the invention

The invention relates to the methanesulfonic acid addition salts of Imatinib and to the processes for their preparation. In particular, the invention relates to the process for the preparation of Imatinib methanesulfonate α-crystal form.

The related art

Imatinib, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-yloamino]phenyl]benzamide, has been disclosed in the European Patent Application EP 0564409 A1 as a pharmacologically active substance of anti-tumour activity, especially useful in the treatment of diseases which respond to an inhibition of the receptor tyrosine kinase.

A novel crystal modification of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-piperidin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide, i.e. the β-crystal form, has been described in the publication of the International Patent Application WO 99/03854. This β-crystal form could be obtained, *inter alia* from the less thermodynamically stable α-crystal

form by triturating a suspension of the latter in a polar solvent, especially an alcohol, such as methanol. The β-crystal form could be also obtained directly from the free base by treating a suspension of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-yloamino]phenyl]benzamide with methanesulfonic acid in methanol, concentrating the obtained solution and inoculating it with seeds of the β-crystal form.

In WO 99/03854, the authors have made a general note that the α-crystal form could be obtained, e.g. by precipitating out a methanesulfonate acid addition salt from its solution in a solvent other than alcohol, such as methanol, and without adding any seeds of the β-crystal form. The method of preparing the α-crystal form, provided in Example 1 is as follows:

(1) a suspension of the free base in ethanol is treated with methanesulfonic acid and the solution of the obtained salt is refluxed for 20 min.;

(2) the solution obtained as above is concentrated to a half of its initial volume and the precipitate that has formed is filtered at 25°C, to give the filtration product A;

(3) the filtrate is evaporated to dryness, the filtration product A is then added to the

residue followed by appropriate volume of ethanol and water and the mixture is refluxed until completely dissolved;

(4) after cooling the solution slowly down to 25°C, the α-crystal form is isolated by filtration.

However, attempts to reproduce Example 1 have proven that the above disclosure is insufficient for preparing the Form α selectively and repeatedly.

On repeating the procedure of the Example 1 with the use of anhydrous ethanol (i.e. ethanol containing 0.1% (m/v) of water), the authors of the present application have found that the filtration product A, after combining it with the residue after concentrating the filtrate is not completely dissolved in the specified volume of water and ethanol. Crystals of the salt precipitated from the solution obtained after filtering undissolved crystals and allowed to cool down steadily to room temperature. However, as it results from the analysis by X-ray powder diffraction based upon the data provided in WO 99/03854, the crystals are the β-crystal form. On the other hand, in case of using ethanol containing 4.8% (m/v) of water the solution concentrated to a half of its volume does not crystallize easily and the final solution of the salt does not crystallize without inoculation even after 36 hours since it has been cooled down to about 16°C.

Furthermore, the method for preparing the α-crystal form, presented in the publication WO 99/03854, requires several unit operations, such as isolation of crude methanesulfonate crystals from the reaction mixture, concentration of the solution by evaporating ethanol and re-suspending the methanesulfonate salt in the same solvent.

Moreover, the authors of the present invention have found that without inoculating the reaction mixture crystallization of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide has a random nature, i.e., the Form α, the Form β or mixtures thereof are being obtained randomly disregarding the reaction conditions.

Therefore, it has been necessary to find a selective and reproducible method of preparing the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide. Furthermore, it would be desirable to design a method suitable for performing in a single reaction vessel.

The problem has been solved by a method disclosed in the Polish Patent Application No. P-366885 of April 2, 2004, in which the reaction of equimolar amounts of methanesulfonic acid with 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-

ylamino)phenyl]benzamide is carried out in ethyl alcohol or in a mixture of ethyl alcohol with another C_1-C_4 aliphatic alcohol, then an ester of a carboxylic acid and C_1-C_4 aliphatic alcohol is added to the reaction mixture, the whole mixture is cooled down to the internal temperature A, seeded with the crystals of α-crystal form and the resulting reaction mixture is left with stirring at internal temperature B for the time necessary for crystallization of the α-crystal form.

Although the method allows for obtaining the pure α-crystal form, it requires using two different solvents, the second of which (an ester of a carboxylic acid and C_1-C_4 aliphatic alcohol) causes precipitation out of the acid addition salt from the reaction mixture. Furthermore, the method requires inoculating the reaction mixture with the seeds of the α-crystal form and the yield of crystallisation hardly exceed 80%.

The present invention is based upon the experimental finding that in some cases, when certain solvents or mixtures thereof are used, the obtained α-crystal or β-crystal forms of Imatinib methanesulfonate or a mixture thereof additionally contains morphologically different, unidentified crystals. Dissimilarity of the crystals and known forms of the

methanesulfonate has been confirmed by the X-ray structure analysis and the IR spectrum.

Analysis of the isolated crystals by the proton magnetic resonance (NMR) method has demonstrated that they are the acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide with two molecules of methanesulfonic acid, i.e. Imatinib dimethanesulfonate (dimesylate).

The discovery of a simultaneous formation of the different crystalline forms of Imatinib monomethanesulfonate and dimethanesulfonate, depending on crystallization conditions, has allowed for developing a more selective method of preparing the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide, hereinafter referred to Imatinib monomesylate.

It was found that by using not more than 0.99 equivalent of methanesulfonic acid per 1.00 equivalent of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide in the addition reaction allows for obtaining a the α-crystal form of Imatinib monomesylate that is essentially free of Imatinib monomesylate β-crystal form as well as of Imatinib dimesylate crystalline

forms in the amounts detectable by spectroscopic methods.

Unexpectedly, it was found also that by restricting the stoichiometric ratio of the reactants it is possible to extend possibility of obtaining the essentially pure α-crystal form of Imatinib monomesylate, in particular to extend the range of usable solvents or their mixtures of a definite composition. However, in some cases, e.g. in case of using a mixture of ethanol and methyl-*tert*-butyl ether, formation of Imatinib dimesylate could not be avoided. It seems that in case of certain solvents, the equilibrium between Imatinib free base, Imatinib monomesylate and Imatinib dimesylate is attained, despite using less than 1.00 equivalent of methanesulfonic acid per 1.00 equivalent of Imatinib:

$$\text{Imatinib} \rightleftharpoons \text{Imatinib.MeSO}_3\text{H} \rightleftharpoons \text{Imatinib.(MeSO}_3\text{H)}$$

Therefore, a method has been developed that under certain conditions allows for eliminating the need of seeding the mixture with α-crystal form by using the reagents in the stoichiometric ratio less than 1.00 : 0.99 together with the appropriate solvents. Addition of the precipitating solvent, like an ester, is also not necessary.

Description of the invention

The process of the invention for the preparation of an acid addition salt of methanesulfonic acid of 4-

(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide in the α-crystal form comprises:

a) carrying out the addition reaction of methanesulfonic acid and 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a solvent selected from the group consisting of C_2-C_6 aliphatic alcohols or the mixtures thereof, optionally with the addition of the other C_1-C_4 aliphatic alcohol;

b) adding, if necessary, a solvent selected from the group consisting of the esters of lower carboxylic acids and C_1-C_4 aliphatic alcohols;

c) optionally inoculating the reaction mixture with the α-crystal form;

d) stirring the reaction mixture for the time necessary for crystallization of the α-crystal form;

e) isolating the α-crystal form from the reaction mixture.

In the preferred embodiment of the invention, the acid addition reaction is carried out using not more than 0.99 equivalent, especially from 0.95 to 0.99 equivalents of methanesulfonic acid per 1.00 equivalent

of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide.

Solvents, suitable for the addition reaction and crystallization are those selected from the group comprising n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, *tert*-butyl alcohol and the mixtures thereof, particularly the mixtures containing ethyl alcohol.

In one variant of this embodiment of the invention, the addition reaction is carried out in the mixture of solvents consisting of from 0 to about 50% of ethyl alcohol and from 50% to 100% of *n*-propyl alcohol (v/v).

In the other variant of this embodiment of the invention, the addition reaction is carried out in the mixture of solvents consisting of from 0 to about 50% of ethyl alcohol and from 50% to 100% of isopropyl alcohol (v/v).

In still another variant of this embodiment of the invention, the addition reaction is carried out in the mixture of solvents containing from 0 to about 50% of ethyl alcohol and from 50% to 100% of *n*-butyl alcohol (v/v).

In still another variant of this embodiment of the invention, the addition reaction is carried out in the mixture containing from 0 to about 50% of ethyl alcohol and from 50% to 100% of *tert*-butyl alcohol (v/v).

Appropriate selectivity of crystallization could be attained also by using only one alcohol, preferably *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol or *tert*-butyl alcohol.

Usually, from 15 to 50 volume parts of an alcohol or a mixture of alcohols are used in the addition reaction per 1 weight part of Imatinib base, depending on the used solvent system. The solvent can be introduced in one portion at the beginning of the addition reaction or in parts during its course.

In the second embodiment of the invention, the equimolar amounts of the reagents are used. In this case, the necessary condition of the selective crystallization of α-crystal form of Imatinib monomesylate is, upon the completion of the acid addition reaction, adding to the reaction mixture of the ester of lower carboxylic acid and C_1-C_4 aliphatic alcohol (ester-type solvent). As the preferred ester-type solvents can be mentioned alkyl esters of formic acid, acetic acid and propionic acid, especially ethyl acetate. The advantageous effect of crystallization is also gained with the addition of isopropyl acetate. The volume of the ester added is at least equal to the volume of alcoholic solvents used.

As has been mentioned above, in the preferred embodiment of the invention the addition reaction is carried out using from 0.95 to 0.99 equivalents of

methanesulfonic acid per 1.00 equivalent of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl] benzamide.

The reaction mixture is stirred while maintaining internal temperature of the mixture within the range from room temperature to the boiling temperature of the solution. After addition of the calculated amount of methanesulfonic acid to the suspension of Imatinib base in the selected solvent, one can optionally add an additional amount of the same or another solvent.

Addition of an ester-type solvent in this embodiment is not necessary but it increases the yield of α-crystal form of Imatinib monomesylate and allows for reducing the volume of the solvent used for suspending Imatinib base. Thus, the method disclosed in the Polish Patent Application No. P-366,885 is now improved by applying the above provided preferred ratio of reagents. The effect is evidenced in the Examples 8-11 hereby incorporated to the present application.

Crystallization can be initiated by inoculating the reaction mixture with crystal seeds of α-crystal form. However, in many cases inoculation is not necessary, because the solvent system and the molar ratio of reagents that have been used are favorable for spontaneous crystallization of the acid addition salt of methanesulfonic acid and 4-(4-methylpiperazin-1-

ylmethyl)-N-[4-methyl-3- [4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide in the α-crystal form.

The mixture is cooled down and then left with continuous stirring for the time necessary for crystallization of the α-crystal form, i.e. usually for 3-5 hours. The crystalline solid is isolated in a way known to those skilled in the art, washed, e.g. with ethyl acetate and dried at first at room temperature in the air and then at room temperature or at elevated temperatures, e.g. about 60°C, under reduced pressure.

The process according to the invention is the selective and reproducible method for preparing the essentially pure α-crystal form of the acid addition salt of methanesulfonic acid and 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide.

For the purposes of this invention, the term "essentially pure α-crystal form of Imatinib monomesylate" is to be understood as the α-crystal form of the methanesulfonic acid addition salt of methanesulfonic acid and 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide, that contains no admixtures of other crystalline forms of Imatinib monomesylate or any other crystalline solids in amounts detectable by the conventionally used analytical methods, i.e. the

form that contains less than 2%, preferably less than 1% by weight of the β-crystal form of Imatinib monomesylate or any other crystalline solids.

The crystalline form of the acid addition salt of methanesulfonic acid and 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide, obtained by the method according to the invention, has been analyzed by IR spectroscopy, X-ray powder diffraction and differential scanning calorimetry and the obtained results were compared to data for the reference β-crystal form, obtained by the method described in WO 99/03854, Example 1, and to analytical data for both forms provided in the publication of the aforementioned patent application.

The IR spectrum of the α-crystal form, measured using a KBr pellets technique, is essentially different from that of the β-Form within the whole range of the spectrum (4,000 - 400 cm^{-1}), as it is showsn in Table 1.

Table 1. FT-IR spectra (KBr pellets): comparison of characteristic bands for the α- and β-crystal forms of Imatinib monomesylate

α-crystal form		β-crystal form	
ν, cm^{-1}	Intensity*	ν, cm^{-1}	Intensity*
3257	m	3336	m
3033 - 3010	m	3006 – 2946	m
2824 - 2782	m	2801 – 2758	m
2706 - 2492	m - w	-	
1660	s	1656	s

α-crystal form		β-crystal form	
ν, cm^{-1}	Intensity*	ν, cm^{-1}	Intensity*
		1596	s
1572	s	1574	s
1527	s	1534	s
		1482	s
1447	s		
1321	m	1310	m
1221	s	1224	s
1161	s	1168	s
1037	s	1037	s
807	m	815	m
772	m	803	m
		765	m
749	m	751	m
555	m	549	m
		521	m

* s = strong, m =moderate, w = weak

The comparison of the IR spectra of the α-crystal form obtained by the method according to the invention and the reference β-crystal form within the whole range of the spectrum is presented on Fig. 1.

Fig. 2 presents a comparison of DSC curves of the crystalline Forms α and β. Endothermic peaks, characteristic for the melting process of the substance are visible on the curves of the α- and β-crystal forms. Compared to those of the α-crystal form, the melting point of the β-crystal form is lower, and corresponding melting enthalpy is larger. The melting points and enthalpies of both crystalline forms are showsn also in Table 2. The melting points have been determined by two methods: (i) as the „extrapolated peak" i.e. the intersection point of tangents to the peak curve and (ii) as „the onset", i.e. the

intersection point of tangents to the baseline and to the rising line of the peak.

Table 2. DSC: Comparison of the melting points and melting enthalpies of the α- and β-crystal forms of Imatinib monomesylate

	Form α	Form β
Melting point, °C (by *peak extrapolation*)	224,3	216,5
Melting point, °C (by *onset*)	223,7	214,7
Melting enthalpy, J/g	108	127

Figs. 3 and 4 represent characteristic X-ray powder diffraction diagrams of the α- and β-crystal forms of Imatinib monomesylate, where intensity of the relative diffraction peaks of CuKα radiation, and refraction θ are showsn as a function of interplanar distances d, at the refraction angles 2θ from 3° to 40°, scanning rate 0.5 deg/min and counting accuracy of 0.03 deg. The comparison of positions and intensities of main diffraction peaks (of relative intensity over 20% and some weaker peaks suitable for identifying the particular crystalline form) for the crystalline Forms α and β is presented in Tables 3 and 4.

Table 3. X-ray powder diffraction diagrams of the α-crystal form (main diffraction peaks)

No. of the peak	d (Å)	2θ (°)	I/I_0 (%)

No. of the peak	d (Å)	2θ (°)	I/I_0 (%)
1	**17.89**	**4.9**	**10.4**
2	8.41	10.5	53.6
3	5.93	14.9	37.1
4	5.36	16.5	26.3
5	5.00	17.7	51.9
6	4.89	18.1	64.6
7	**4.75**	**18.6**	**100.0**
8	**4.64**	**19.1**	**72.2**
9	4.17	21.3	61.5
10	4.10	21.6	73.8
11	3.92	22.7	23.1
12	**3.83**	**23.2**	**32.3**
13	3.74	23.8	29.2
14	3.57	24.9	76.1
15	3.25	27.4	22.0
16	3.18	28.0	21.7
17	**3.12**	**28.6**	**72.4**

Table 4. X-ray powder diffraction diagrams of the β-crystal form (main diffraction peaks)

No. of the peak	d (Å)	2θ (°)	I/I_0 (%)
1	**15.28**	**5.8**	**8.2**

No. of the peak	d (Å)	2θ (°)	I/I_0 (%)
2	**10.55**	**8.4**	**4.5**
3	**9.12**	**9.7**	**19.1**
4	6.37	13.9	30.8
5	**5.09**	**17.4**	**59.3**
6	4.89	18.1	66.6
7	4.70	18.9	21.2
8	**4.45**	**19.9**	**55.8**
9	**4.32**	**20.5**	**100.0**
10	4.22	21.0	75.3
11	4.03	22.0	65.4
12	3.92	22.7	34.8
13	3.75	23.7	32.8
14	3.52	25.3	20.9
15	3.33	26.8	25.0
16	3.01	29.7	31.9
17	2.90	30.8	25.6

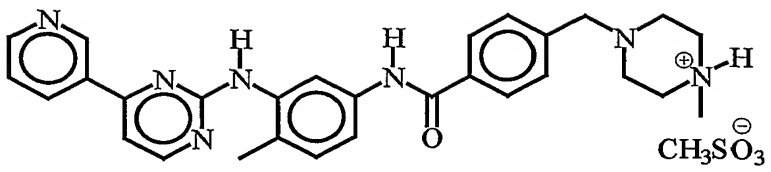
In Tables 3 and 4, the characteristic peaks that could be suitable for identifying both forms in their mixtures and for determining their crystalline purity, are marked with bold numbers. The peaks, characteristic for the α-crystal form are observed at the 2θ angles of about: 4.9; 18.6; 19.1; 23.2 and 28.6°, and those for the β-crystal form at the 2θ angles of about: 5.8; 8.4; 9.7; 17.4; 19.9 and 20.5°.

Analysis of the data obtained by X-ray powder diffraction, IR spectroscopy and differential scanning calorimetry shows that the method according to the invention provides the α-crystal form of Imatinib

monomesylate that is essentially free of any admixtures of the β-crystal form or any other crystalline forms.

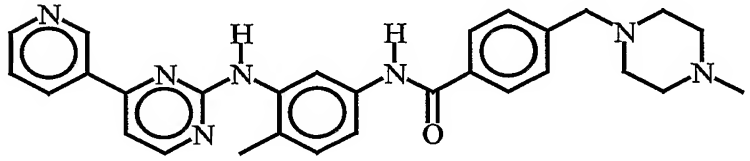
As mentioned above, crystallization of the α-crystal form obtained in the addition reaction using equimolar amounts of methanesulfonic acid and 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pirimidin-2-ylamino)phenyl]benzamide in certain solvents is very often accompanied by formation of a crystalline impurity. This has been identified by the Inventors as Imatinib dimesylate on the base of proton magnetic nuclear resonance (^{1}H NMR (DMSO-d_6), with shifts δ (ppm): 10.28 (1H, s, NH), 9.38 (1H, d, J=1.8 Hz), 9.07 (1H, s, NH), 8.81 (1H, dd, J=5.0 i 1.4 Hz), 8.73 (1H, dt, J=8.1 i 1.8 Hz), 8.57 (1H, d, J=5.1 Hz), 8.14 (1H, d, J=1.8 Hz), 8.05 (2H, d, J=8.2 Hz), 7.74 (1H, dd, J=8.0 i 5.1 Hz), 7.63 (2H, d, J=8.1 Hz), 7.51 (1H, dd, J=8.2 i 2.1 Hz), 7.50 (1H, d, J=5.1 Hz), 7.24 (1H, d, J= 8.5 Hz), 4.17 (2H, s), 2.9-3.7 (8H, br m), 2.87 (3H, s, N-CH_3), 2.45 (6H, s, 2xCH_3, 2x$MeSO_3H$), 2.25 (3H, s, Ar-CH_3).

Imatinib dimesylate is thus formed in the reaction of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide with two equivalents of methanesulfonic acid.



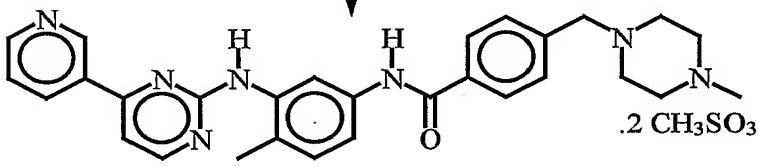
mesylan Imatinibu

+ CH_3SO_3H



Imatinib

+ 2 CH_3SO_3H



dimesylan Imatinibu

The Inventors have succeeded in isolating dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pirimidin-2-ylamino)phenyl]benzamide (Imatinib dimesylate) in its crystalline form as an impurity of one of the crystalline forms of Imatinib monomesylate as well as determining its physicochemical properties. The compound was then synthesized which has allowed for proving existence of two polymorphs of these compounds.

Another aspect of the invention is therefore a novel methanosulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-

3-yl)pyrimidin-2- ylamino)phenyl]benzamide that comprises two molecules of the acid per one molecule of Imatinib, i.e. Imatinib dimesylate.

Imatinib dimesylate crystallizes in two distinct crystalline forms, hereinafter referred to as the Form I and Form II, depending on the solvents used for crystallization and crystallization conditions (with, or without crystal seeds). Under certain conditions, it crystallizes as a mixture of both polymorphs in the weight ratio of approximately 1:1.

The crystalline Forms I and II of Imatinib dimesylate and their mixture can be easily identified and distinguished from each other or from Imatinib monomesylate polymorphs by differential scanning calorimetry (DSC), infra-red absorption spectrum with Fourier transformation (FTIR) and X-ray powder diffractometry (XRPD).

Characteristic endothermic peaks, corresponding to melting of the substances are visible on the DSC curves of the crystalline Forms I and II of Imatinib dimesylate. The melting point of the Form I is higher than that of the Form II while melting enthalpies are comparable. Two peaks that reflect melting of both forms are visible on the DSC curve of the crystalline mixture. Melting temperatures and enthalpies of the mixture of both forms are presented in Table 5.

Table 5. DSC: Comparison of melting temperatures and enthalpies of the crystalline Forms I and II and the mixture of both Forms of Imatinib dimesylate

	Form I	Form II	Mixture Forms I and II
Melting point, °C (by *peak extrapolation*)	227,2	211,0	208,8 222,2
Melting point, °C (by *onset*)	225,3	205,6	202,0 216,6
Melting enthalpy, J/g	100,7	103,5	-

Fig. 5 shows the characteristic X-ray diffraction diagram of Form I of Imatinib dimesylate, Fig. 6 shows the characteristic X-ray diffraction diagram of Form II of the compounds and Fig. 7 shows the characteristic X-ray diffraction diagram of the crystalline mixture of these Forms.

Positions and intensities of diffraction peaks of the crystalline Forms I and II of Imatinib dimesylate and of their mixture are presented in Tables 6, 7 and 8 (the peaks of intensity over 20% are marked with bold figures).

Table 6. X-ray powder diffraction diagram of Imatinib dimesylate Form I

d [Å]	2θ [°]	I/I_0 [%]
17.71	4.98	2.1
10.52	8.47	4.2
9.30	9.49	3.9

d [Å]	2θ [°]	I/I_0 [%]
8.89	9.93	17.2
8.38	10.54	1.6
8.06	10.99	2.7
7.04	12.56	3.4
6.75	13.09	6.3
6.36	13.91	1.8
5.92	14.94	8.8
5.56	15.91	5.2
5.41	16.35	18.9
5.22	**16.94**	**27.4**
4.94	17.93	7.7
4.47	**19.80**	**100.0**
4.41	**20.08**	**41.7**
4.32	**20.51**	**32.2**
4.17	**21.28**	**20.2**
4.10	**21.65**	**27.2**
4.04	**21.98**	**30.0**
3.91	**22.70**	**43.0**
3.85	**23.07**	**29.3**
3.62	24.50	17.8
3.57	24.90	13.4
3.39	26.22	17.9
3.26	27.28	14.7

d [Å]	2θ [°]	I/I_0 [%]
2.78	32.09	5.5

Table 7. X-ray powder diffraction diagram of Imatinib dimesylate Form I

d [Å]	2θ [°]	I/I_0 [%]
8.89	9.93	13.6
6.19	14.28	7.7
6.02	14.68	15.0
5.68	15.57	15.7
5.50	16.08	11.3
5.14	**17.23**	**22.7**
5.02	**17.62**	**81.4**
4.73	**18.72**	**100.0**
4.45	**19.90**	**39.1**
4.38	**20.23**	**28.3**
4.17	**21.25**	**51.0**
4.11	**21.59**	**84.6**
4.02	**22.05**	**48.0**
3.95	**22.44**	**41.3**
3.80	**23.38**	**66.3**
3.75	**23.68**	**40.9**
3.63	**24.48**	**30.0**
3.50	**25.41**	**28.7**
3.41	**26.10**	**44.5**
3.14	**28.39**	**37.5**
2.79	32.02	13.9
2.68	33.38	12.5

Table 8. X-ray powder diffraction diagram of the mixture of Forms I and II of Imatinib dimesylate

d [Å]	2θ [°]	I/I_0 [%]

d [Å]	2θ [°]	I/I_0 [%]
10.41	8.48	4.0
9.31	9.48	4.5
8.90	9.92	17.5
8.39	10.53	2.2
8.04	10.99	2.3
5.91	14.95	9.7
5.68	15.58	6.0
5.41	16.34	18.2
5.23	**16.91**	**27.2**
5.03	**17.60**	**28.5**
4.74	**18.69**	**34.3**
4.48	**19.78**	**100.0**
4.32	**20.50**	**33.8**
4.10	**21.60**	**51.9**
4.03	**22.00**	**42.6**
3.91	**22.70**	**50.3**
3.85	**23.07**	**34.9**
3.63	**24.49**	**26.4**
3.50	25.39	17.0
3.40	**26.13**	**26.2**
3.26	**27.25**	**24.6**
2.78	32.09	9.5

As shown in Table 9, the IR spectrum of Imatinib dimesylate Form I obtained by the KBr pellet technique is noticeably different from that of Form II within the whole range of wavelengths (4,000 - 400 cm^{-1}). Bands, corresponding to both Forms I and II are clearly visible in the IR spectrum of the mixture of these forms.

Table 9. FT-IR spectrum (KBr pellets): Comparison of the characteristic bands, distinguishing the crystalline Forms I and II of Imatinib dimesylate and their mixture

Form I		Form II		Mixture of Forms I and II	
ν, cm^{-1}	Intensity*	ν, cm^{-1}	Intensity*	ν, cm^{-1}	Intensity*
3435	m-w (broad band)	3435	m.	3436	m.
3276	m	3237	m-w	3275	m.
3008	m	3096	m-w	3008	m.
2483	m (broad band)	3007	m.	2484	m (broad band)
		2468	m (broad band)		
1647	s	1666	m-s	1666	
				1647	m.
		1617	m.		
		1603			
1586	s	1576	m.	1577	s
1577					
1554	m			1554	w
1537	s	1537	s	1537	s
		1529			
		1493	m.	1495	w
1454	s	1453	s	1453	s
1422	m	1437		1422	m.
		1397	m.	1398	m.
		1372	m.	1373	m.
1325		1337	m.	1336	
1311	m	1304	m-w	1311	m.
1295		1283	m-w	1297	
1224	s	1225	s	1224	s
1149	s	1149	s	1150	s
1039	m	1026	s	1039	s
952	m-w	945	m.	948	m.
		910	w	911	w
892				892	w
870	m-w	865	m.	866	m.
852					
798	m	806	m.	806	m.
772	m	774	m.	773	m.
706		710	m-w	708	
691		666	m.	691	
674		642	w	667	m-w
647	m-w	619	m.	647	
611		614		615	
583					
553	s	552		553	m-s
532	m	538	m.	536	m
524		524		524	
478		452	w	454	w
459	w	431		429	
427					

*Band intensity: w -weak, m - moderate, s – strong

Yet another aspect of the invention is the crystalline Form I of the dimethanosulfonic acid addition salt 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide (Imatinib dimesylate).

The crystalline Form I of Imatinib dimesylate is characterized by the peaks of intensity over 20% at 2θ angles in the X-ray powder diffraction diagram of approximately 16.94, 19.80, 20.08, 20.51, 21.28, 21.65, 21.98, 22.70 and 23.07°.

Form I is formed in such solvent systems as, e.g. ethyl alcohol/*tert*-butyl-methyl ether, ethyl alcohol/ethyl acetate, isopropyl alcohol.

Another aspect of the invention is the crystalline Form II of the dimethanosulfonic acid addition salt 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide (Imatinib dimesylate).

The crystalline Form II of Imatinib dimesylate is characterized by the peaks of intensity over 20% at 2θ angles in the X-ray powder diffraction diagram of approximately 17.23, 17.62, 18.72, 19.90, 20.23, 21.25, 21.59, 22.05, 22.44, 23.38, 23.68, 24.48, 25.41, 26.10 and 28.39°.

Form II is Formed in such solvent systems as, e.g. ethyl alcohol/acetone, methyl alcohol.

In some cases, Imatinib dimesylate crystallizes as a mixture of the Forms I and II in the weight ratio approximately 1:1 in the same solvents as above, e.g. in ethyl alcohol, ethyl alcohol/ethyl acetate, but without seeding the reaction mixture with crystal seeds.

Yet another aspect of the invention is the mixture of the crystalline Forms I and II of the methanosulfonic acid addition salt 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in the weight ratio about 1:1, characterized by the peaks of intensity over 20% at 2θ angles in the X-ray powder diffraction diagram of approximately: 16.91, 17.60, 18.69, 19.78, 20.50, 21.60, 22.00, 22.70, 23.07, 24.49, 26.13 and 27.25°.

4-(4-Methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide dimesylate has advantageous physicochemical properties, it is thermodynamically stable and non-toxic, hence as a pharmaceutically acceptable salt (Handbook of Pharmaceutical Salts,. P.H. Stahl, C.G. Wermuth (eds.), Verlag Helvetica Chimica Acta, 2002) it could be used as an active ingredient in pharmaceutical compositions having anti-neoplastic activity.

For therapeutic applications, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-

3-yl)pyrimidin-2-ylamino)phenyl]benzamide dimesylate is formulated into pharmaceutical compositions containing a therapeutically efficacious amount of the salt in combination with at least one pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical composition according to the invention is administered to a patient in need of such treatment in a suitable pharmaceutical dosage form, by the route appropriate for the dosage form, e.g. orally or parenterally (intravenously, intramuscularly or subcutaneously).

Selection of the dose and dosage regimen depends on the type of disease, age, weight and condition of the patient and they could be determined by a specialist on the basis of known procedures of treatment and prevention of such diseases. Preferred dose of the salt according to the invention can be 100-500 mg, calculated on free 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide. The dose can be administered to the patient once per day or several times per day, separately or in a combination with other medicinal substances. Such substances can be administered concurrently in a Form of a single preparation or as different preparations. Alternatively, the preparations could be administered subsequently in the order and time intervals determined by a specialist.

The pharmaceutical ingredient according to the invention can be Formulated in various combinations, well known to those skilled in the art., such as those described, e.g., in Remington's Pharmaceutical Sciences, XVIth ed., Mack Publ. Co., 1980.

The pharmaceutical preparations for oral administration comprise tablets, drageés, powders, granules, pellets or capsules containing solid, pharmaceutically acceptable excipients such as corn starch, lactose, sucrose, sorbitol, talc, mannitol or dicalcium phosphate. The tablets or granules can be coated or otherwise processed in order to obtain a dosage Form providing advantageous, prolonged activity. Numerous substances can be used for preparing such protecting layers comprise various polymeric acids and mixtures thereof, with such substances as shellac, cetyl alcohol or cellulose acetate.

It is reasonable to consider administration of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide dimesylate containing pharmaceutical preparations in the Form of preparations for injection or infusions. Such preparations comprise sterile aqueous, aqueous-organic and non-aqueous solutions, suspensions, dry substances and tablets for preparing solutions or for implantation. Excipients that ensure a uniForm

distribution of the medicinal substance in the liquid Form, used for preparing suspensions comprise polysorbates, lecithin, copolymers of polyoxyethylene with polyoxypropylene, peptizing agents such as phosphates, polyphosphates and citrates, water-soluble polymers such as carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, resins or gelatin. The injectable compositions can contain pharmaceutically acceptable excipients such as pH-adjusting agents and buffers, tonicity modifiers and preservatives. The dry substances are designated for preparation of solutions or suspensions *ex tempore* by diluting the substances using appropriate solvents.

Description of Drawings

Fig. 1 presents a comparison of IR spectra of Imatinib monomesylate α- and β-crystal forms.

Fig.2 presents a comparison of DSC curves of Imatinib monomesylate α- and β-crystal forms.

Fig. 3 presents X-ray powder diffraction diagram of the of Imatinib monomesylate α-crystal form.

Fig. 4 presents X-ray powder diffraction diagram of the of Imatinib monomesylate β-crystal form.

Fig. 5 presents the DSC curve of Imatinib dimesylate crystalline Form I.

Fig.6 presents the DSC curve of Imatinib dimesylate crystalline Form II.

Fig.7 presents the DSC curve of the mixture of Imatinib dimesylate crystalline Forms I and II (obtained directly from a crystallization experiment).

Fig. 8 presents a characteristic X-ray powder diffraction diagram of Imatinib dimesylate crystalline Form I.

Fig. 9 presents a characteristic X-ray powder diffraction diagram of Imatinib dimesylate crystalline Form II.

Fig.10 presents a characteristic X-ray powder diffraction diagram of the mixture of Imatinib dimesylate crystalline Forms I and II.

Fig. 11 presents the IR spectrum of Imatinib dimesylate crystalline Form I.

Fig. 12 presents the IR spectrum of Imatinib dimesylate crystalline Form II.

Fig. 13 presents the IR spectrum of the mixture of Imatinib dimesylate crystalline Forms I and II.

Experimental part

DSC analyses were performed using the Mettler Toledo DSC 822 apparatus in 40 µL aluminum crucibles that were initially compressed hermetically and then punctured. The analyses were performed under a stream of nitrogen at the flow rate of 60 mL/min. within the temperature range 30-260°C at the heating rate of

5°C/min. in the dynamic phase, preceded by an isothermal phase (30°C for 5 min.) in order to stabilize the oven temperature at the initial measurement value.

The melting points have been determined by two methods: (i) as the „extrapolated peak" i.e. the intersection point of tangents to the peak curve and (ii) as „the onset", i.e. the intersection point of tangents to the baseline and to the rising line of the peak.

The X-ray powder diffraction (XRPD) diagrams were obtained using a Mini Flex powder diffractometer supplied by Rigaku. The measurement parameters were as follows:

- range of 2θ angle : 3.0 - 40.0°,
- $CuK\alpha_1$ radiation wavelength λ=1.54056 Å,
- scanning rate: 0.5° per minute,
- accuracy $\Delta 2\theta$ = 0,03°.

Infra-red (IR) spectra were obtained from pellets pressed with KBr using a FT-IR spectrometer Perkin Elmer type BX within the range of 4,000 - 400 cm^{-1} and resolution of
4 cm^{-1}.

The invention is further illustrated by the following, non-limiting, Examples.

Examples

A. Imatinib monomesylate

Example 1

The suspension of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide 3,802 g (0.01 mole) in anhydrous ethyl alcohol (85 mL) was heated with stirring to 75°C, and thereafter methanesulfonic acid (0.5 mL, 0.01 mole) was slowely added dropwise. The mixture was further heated at 75°C for 10 min. Ethyl acetate (85 mL) was added dropwise and the mixture was cooled down to 30°C while being stirred. The seeds of α-crystal form (17 mg) were added and then the mixture was cooled down and stirred at 13 to 20°C for 4 h. The crystals were filtered off, washed with 40 mL of ethyl acetate and dried. Yield: 2,954 g (65.0%); the product that has been identified as Imatinib mesylate α-crystal form.

Examples 2-7

Imatinib mesylate α-crystal form has been prepared according to the general method described in the Example 1, using Imatinib base : methanosulfonic acid = 1:1 (mole/mole), with different crystallization parameters.

Table. Crystallization parameters

No.	Solvent in the	Ester-type	Temp.	Temp.	Crystal-	Yield

	addition reaction (mL)	solvent (mL)	A (°)	B (°)	lization time (h)	(g, %)
1	ethyl alcohol (85)	ethyl acetate (85)	30	13-20	4	2,954 65.0%
2	ethyl alcohol (75)	ethyl acetate (100)	30	15-18	3,40	2,957 65.1%
3	ethyl alcohol (85) + water (0,5)	ethyl acetate (85)	25	17-21	3,50	2,733 60.1%
4	ethyl alcohol (85)	isopropyl acetate (85)	25	16-18	4,40	3,790 83.4%
5	ethyl alcohol (40) + methyl alcohol (45)	isopropyl acetate (85)	25	16-20	4,50	2,229 49.1%
6	ethyl alcohol (65) + isopropyl alcohol (20)	ethyl acetate (85)	24	16-20	4,20	3,951 87.0%
7	ethyl alcohol (85)	ethyl acetate (85)	21	20-21	5	3,168 69.7%

Example 8

Methanesulfonic acid (0.73 g, ca. 0.99 eq.) was added, with stirring, to a suspension of Imatinib (3.802 g, 0.01 mol) in ethanol (63 mL) heated previously to 65°C and the mixture was stirred for 10 min. Ethyl acetate (63 mL) was then added slowly dropwise and the mixture was cooled down to 34°C while being stirred. The seeds of the α-crystal form (50 mg) were added and then the mixture was cooled down and

stirred at room temperature for 4.5 h. The crystals were filtered off, washed with 30 mL of ethyl acetate and dried under reduced pressure at room temperature. Yield: 3.699 g (81.4%) of the product that has been identified as Imatinib monomesylate α-crystal form.

Example 9

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (39.96g, 0.08 mol) in the mixture of ethanol (890 mL) and ethyl acetate (200 mL) heated previously to 65°C. The solution was stirred for 10 min. and then ethyl acetate (690 mL) was added slowly dropwise. The mixture was slowly cooled down to 39°C while being stirred and then 1.215 g of the seeds of the α-crystal Form was added and the mixture was slowly cooled down to 22°C. Next, the mixture was left without stirring at room temperature (ca. 19°C) for two days. The product was filtered off and washed with 100 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature. Yield: 44.43 g (93.1%) of the product.

Example 10

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (10.647 g) in ethyl alcohol (173 mL) heated previously to 65°C and the mixture was stirred for 5 min. The seeds of the α-crystal Form (0.279 g) were added to the solution at

approx. 44°C followed by dropwise addition of isopropanol (65 mL) and ethyl acetate (238 mL). Stirring at room temperature (approx. 24-25°C) was continued for 4 hours and then the mixture was left without stirring for 64 h. The product was filtered off and washed with 50 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 11.85 g (93.1%) of α-crystal form of Imatinib monomesylate.

Example 11

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (37.997 g) in ethanol (620 mL) heated previously to 75°C. The resulting solution was stirred for 15 min. and then isopropanol (230 mL) and ethyl acetate (750 mL) were added dropwise. The mixture was stirred and slowly cooled down to 31.5°C and then 0.994 g of the seeds of the α-crystal form were added followed by dropwise addition of ethyl acetate (100 mL). The mixture was further cooled down to 22-23°C. Stirring at that temperature was continued for 4 h. Then the mixture was left without stirring overnight at ca. 20°C. The product was filtered off and washed with 100 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 43.814 g (96.5%) of the product.

Example 12

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (3.802 g) in ethanol (85 mL) heated previously to 68°C. After 5 min., isopropanol (85 mL) was added dropwise. The mixture was slowly cooled down with stirring, and 50 mg of the seeds of the α-crystal Form was added at ca. 37°C. The mixture was cooled down to 21°C (in total, the mixture was stirred for approximately 6.5 h since seeding). The mixture was left without stirring overnight at approx. 21°C. The product was filtered off and washed with 25 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 4.393 g (96.7%) of the product.

Example 13

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (39.96g) in the mixture of ethanol (890 mL) and isopropanol (200 mL) heated previously to 65°C. The solution was stirred for 10 min. and then isopropanol (690 mL) was added slowly dropwise. The mixture was slowly cooled down to 39°C while being stirred and then 1.118 g of the seeds of the α-crystal Form was added and the mixture was slowly cooled down to approx. 22°C. Next, the mixture was left without stirring at room temperature (ca. 20°C) for two days. The product was filtered off and washed with 100 mL of ethyl acetate. The crystals were

dried under reduced pressure at room temperature to afford 46.88 g (98.2%) of the product.

Example 14

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (78.56g) in ethanol (1,100 mL) heated previously to 71°C. The solution was stirred for 10 min at 72-75°C and then isopropanol (1,000 mL) was added slowly dropwise to the hot solution. The mixture was slowly cooled down to 45°C and 1.276 g of the seeds of the α-crystal Form was added. After cooling the mixture down to approximately 20°C, it was stirred at this temperature for 3 h. The product was filtered off and washed with 150 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 91.12 g (97.1%) of the product.

Example 15

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (7.604 g) in ethanol (11 mL) heated previously to 69°C. Isopropanol (225 mL) was slowly added dropwise to the resulting solution. The mixture was slowly cooled down with stirring, and 100 mg of the seeds of the α-crystal form was added at ca. 38°C (the solution was slightly turbid). The mixture was cooled down to 21°C (in total, the mixture was stirred for approximately 6.5 h since seeding). The mixture was left without stirring

overnight at approx. 21°C. The product was filtered off and washed with 50 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 8.502 g (93.6%) of the product.

Example 16

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (22.76 g) in ethanol (180 mL) heated previously to 75°C. Isopropanol (820 mL) was slowly added dropwise. The mixture was slowly cooled down with stirring, and at ca. 44°C 0.600 g of the seeds of the α-crystal Form was added. The mixture was cooled down to 21°C (in total, the mixture was stirred for approximately 6.5 h since seeding). The mixture was left without stirring overnight at approx. 21°C. The product was filtered off and washed with 100 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 26.721 g (98.3%) of the product.

Example 17

Methanesulfonic acid (ca. 0.99 eq.) was slowly added, with stirring to a suspension of Imatinib (10.00 g) in the mixture of ethanol (79 mL) and isopropanol (360 mL) heated previously to 45°C and then 0.282 g of the seeds of the α-crystal Form was added. The mixture was cooled down to room temperature for 5 h and then left without stirring at room temperature (approx. 21°C) overnight. The product was filtered off and

washed with 80 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 11.671 g (97.7%) of the product.

Example 18

Methanesulfonic acid (ca. 0.99 eq.) was added at room temperature (24-24.5°C), with stirring to a suspension of Imatinib (10.000 g) in the mixture of ethanol (79 mL) and isopropanol (360 mL). The resulting mixture was heated to 70°C, at which point almost all crystals have dissolved. Next, the mixture was allowed to spontaneous cooling down to room temperature within 3 h 50 min. The mixture was left without stirring overnight at room temperature (22°C). The product was filtered off and washed with 80 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 11.187 g (93.6%) of the product.

Example 19

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib 22.76 g) in ethanol (182 mL) heated previously to 76°C. Isopropanol (250 mL) was added dropwise to the resulting solution and the whole mixture was heated to 70°C. The mixture was slowly cooled down with stirring, and 0.600 g of the seeds of the α-crystal Form was added at ca. 44°C. Next, isopropanol (850 mL) was added dropwise and the mixture was further cooled down to 22°C. Stirring was continued at that temperature for 0.5 h and then the

mixture was left without stirring overnight at approx. 22°C. The product was filtered off and washed with 100 mL of isopropanol and 75 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 26.306 g (96.7%) of the product.

Example 20

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (1.521 g) in isopropanol (75 mL) heated previously to 65°C and then the mixture was stirred and maintained at approx. 65-70°C until the solids dissolved. The mixture was then slowly cooled down with stirring, and 27 mg of the seeds of the α-crystal Form was added at 34°C. Next, the mixture was slowly cooled down to room temperature and stirring was continued for 4.5 h. The product was filtered off and washed with 15 mL of isopropanol. The crystals were dried under reduced pressure at room temperature to afford 1.761 g (96.9%) of the product.

Example 21

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (10.88 g) in isopropanol (536 mL) heated previously to 75°C. The resulting solution was slowly cooled down with stirring, and 0.285 g of the seeds of the α-crystal Form was added at ca. 40°C (slight turbidity). Next, the mixture was cooled down to room temperature (total cooling time 1 h 15 min.). The mixture was left without

stirring overnight at approx. 22°C. The product was filtered off and washed with 100 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature to afford 12.521 g (96.3%) of the product.

Example 22

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (10.023 g) in isopropanol (440 mL) heated previously to 65°C. The mixture was then left to spontaneous cooling down to 22.5°C (approx. 7 h). The product was filtered off and washed with 45 mL of isopropanol. The crystals were dried under reduced pressure at room temperature to afford 11.784 g (98.4%) of the product.

Example 23

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (5.326 g) in n-propanol (230 mL) heated previously to 72°C. The mixture was stirred for 5 min. and cooled down. Seeds of the α-crystal form (100 mg) were added at 30°C. The mixture was further cooled down to approx. 21°C and then stirred at this temperature for 2.5 h. The product was filtered off and washed with 40 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature.

Example 24

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (5.325 g) in n-butanol (230 mL) heated previously to 70°C. The mixture was stirred for 5 min. and cooled down. Seeds of the α-crystal form (105 mg) were added at 38°C. The mixture was further cooled down slowly to approx. 18°C (within 3.5 h). The product was filtered off and washed with 25 mL of isopropanol and 30 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature.

Example 25

Methanesulfonic acid (ca. 0.99 eq.) was added, with stirring to a suspension of Imatinib (5.320 g) in *tert*-butanol (230 mL) heated previously to 70°C. The yellow-orange mixture was maintained at 75-80°C for 1 h, and then cooled down slowly (within 1 h 40 min.) to 27°C. The product was filtered off and washed with 50 mL of ethyl acetate. The crystals were dried under reduced pressure at room temperature.

B. Imatinib dimesylate

Example 26

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C. *tert*-Butyl-methyl ether (MTBE) was added slowly dropwise to the warm solution, until it became turbid

(6 mL). After 1 h of stirring at room temperature, 5 mL of anhydrous ethanol was added and stirring was continued for 4 h. The precipitate was filtered off and washed with 2 mL of anhydrous ethanol and 5 mL of MTBE. The product was dried under reduced pressure at room temperature to afford 0.739 g of Imatinib dimesylate Form I.

Example 27

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C. *tert-B*utyl-methyl ether (MTBE) was added slowly dropwise to the warm solution, until it became slightly turbid (4.5 mL) followed by seeds of the crystalline form I. After 0.5 h of stirring at room temperature, 5 mL of anhydrous ethanol was added and stirring was continued for 1 h. Next, the mixture was heated to approximately 35°C and stirred at this temperature for 1 h, and then at room temperature for 2.5 h. The precipitate was filtered off and washed with 10 mL of anhydrous ethanol. The product was dried under reduced pressure at room temperature to afford 1.370 g of Imatinib dimesylate Form I.

Example 28

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in isopropyl alcohol (70 mL) heated previously to approx.

65°C. The mixture was heated to 70°C and then slowly cooled down. Seeds of the crystalline Form I were added at 65°C and the cooling was continued. After 3 h of stirring at room temperature the yellow precipitate was filtered off and washed with 10 mL of isopropanol. The product was dried under reduced pressure at room temperature to afford 1.967 g of Imatinib dimesylate Form I.

Example 29

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C. 20 mL of ethyl acetate was added slowly dropwise to the warm solution and stirring was continued. The seeds of the Form I were added at 40°C. The mixture was continued at room temperature for approximately 2 h. and the cooling was continued. The product was filtered off and washed with 10 mL of ethyl acetate. The product was dried under reduced pressure at room temperature to afford 1.983 g of Imatinib dimesylate Form I.

Example 30

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C. The mixture was stirred at this temperature for 10 min. Next, the mixture was cooled down to room temperature. After 0.5 h, 20 mL of acetone was added

dropwise and the mixture was stirred at room temperature for 1 h 50 min. Next, another 20 mL of acetone was added dropwise followed by the seeds of the Form I. After 50 min., additional 10 mL of acetone was added dropwise and the mixture was stirred at room temperature for 1 h 20 min. The product was filtered off and washed with 25 ml of acetone and 35 mL of hexane to afford crystals of Imatinib dimesylate Form II.

Example 31

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C and the mixture was stirred at this temperature for 10 min. The mixture was then cooled down to room temperature and 40 mL of acetone was added slowly dropwise. Next, the seeds of the crystal Form II were added to the mixture followed by slow dropwise addition of 10 mL of acetone. The mixture was stirred at room temperature for 3 h. The product was filtered off and washed with 20 ml of acetone. The product was dried under reduced pressure at room temperature to afford crystals of Imatinib dimesylate Form II.

Example 32

A mixture of the products from Examples 5 and 6 (1.551 g) was treated with 25 mL of methanol and the resulting suspension was stirred at room temperature

for 1 h 50 min. Next, the mixture was heated and the resulting solution was slowly cooled down to room temperature. The seeds of the crystalline Form II were added and stirring at room temperature was continued (4 h 40 min. since the mixture was heated). The product was filtered off and washed with a minimal amount of methanol. Next, the product was dried at room temperature under reduced pressure to afford crystals of Imatinib dimesylate Form II.

Example 33

Methanesulfonic acid (0.4 mL) was added dropwise, with stirring to a suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) heated previously to approx. 65°C. Ethyl acetate was added dropwise to the warm solution until a slight turbidity was observed (27 mL). Next, the seeds of the crystal Form II were added and the mixture was stirred at room temperature for 4 h. The product was filtered off and washed with 20 ml of ethyl acetate. The product was dried under reduced pressure at room temperature. A crystalline mixture of the Forms I and II of Imatinib dimesylate was obtained (weight ratio about 1:1).

Example 34

Methanesulfonic acid (0.4 mL) was slowly added dropwise to a stirred suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) at room temperature. The mixture was heated to the boiling point, then 10 mL of

anhydrous ethanol was added and the mixture was again heated to the boiling point and stirred at this temperature for 3 h and 20 min. The product was filtered off and washed with 15 ml of anhydrous ethanol. The product was dried under reduced pressure at room temperature. A crystalline mixture of the Forms I and II of Imatinib dimesylate was obtained (weight ratio about 1:1).

Example 35

Methanesulfonic acid (0.4 mL) was slowly added dropwise to a stirred suspension of Imatinib (1.521 g) in anhydrous ethanol (20 mL) previously heated to 70°C. Ethyl acetate (20 mL) was added slowly to the hot solution and stirring was continued at room temperature. After 3.5 h, the precipitate was filtered off and washed with a mixture of anhydrous ethanol and ethyl acetate (1:1, 20 mL). The product was dried under reduced pressure at room temperature. A crystalline mixture of the Forms I and II of Imatinib dimesylate was obtained (weight ratio about 1:1).